REMARKS

Further to the Request for Continued Examination (RCE), IDS and Preliminary Amendment filed November 16, 2010, Applicant submits this Second Preliminary Amendment for RCE, as well as attached 132 Declaration, CV, and executed toxicology report in Spanish with an English translation.

Applicant notes that Claim 25 was allowed in the Notice of Allowance dated August 16, 2010, which is now pending in the present continued examination.

Additionally, *based on the Preliminary Amendment filed November 16, 2010*, new independent claim 27 has been added as fully supported by the present specification, to recite the combination of ranges of 0.5-1.5% lidocaine, 0.5-1.5% prilocaine, and 0.5-8% tetracaine. New claims 28-31, 33, and 36-48 were also added, as corresponding to, respectively, original claims 1-5, 7-12, 14-15, 17, 19-20, 22, 24 and 26, as provided in the Preliminary Amendment filed on the same day as the original filing of this US non-provisional application. New claims 32 and 35 were also added to recite alternative recitations of ranges of lidocaine, prilocaine and tetracaine, as fully supported by the present specification. Reconsideration and allowance are respectfully requested.

Applicant respectfully notes that the cancellation of claims is without prejudice to their potential filing of the subject matter thereof in a continuation or divisional application at a later time. Applicant does not admit any unpatentability thereof by these presently cancelled claims.

UNEXPECTED RESULTS SHOWN BY THE TRIPLE COMBINATION OF CLAIMED ANESTHETICS OVER THE PREVIOUSLY CITED STATE OF THE ART

The present specification demonstrates to one of ordinary skill in the relevant arts that the presently claimed triple anesthetic compositions are not suggested by the cited state of the art references that disclose single or double anesthetic compositions.

In particular, the present specification provides description, protocols and direct comparative data comparing the different variables (time, amount of anesthetic components, length of application time, occlusion) side by side and one variable at a time. Applicant has demonstrated that the effect is present or can directly attributable to the claimed triple anesthetic compositions based on the fact that this was tested in humans (in fact in 2700 individuals). Applicant has demonstrated that the effect is present in all claimed concentration ranges. To demonstrate that there is an unexpected, surprising, and/or synergistic effect (in the decrease of side effects) with the 3 anesthetics compared to single or the 2-components combinations, the data in the present specification (as well as attached 132 Declaration) shows this by comparing EMLA (lidocaine/prilocaine) and lidocaine/tetracaine, in a way to have the same proportion of each component in all the formulas and the same total amount of anesthetic, where specific unexpected properties are shown as presented below.

Applicant emphasizes the advantage of not needing occlusion compared to the cited state of the art. Applicant has unexpected solved the problem of occlusion by discovering the claimed, more effective anesthetic treatment without necessity of occlusion. How to solve this problem is not described, suggested, or motivated in the cited state of the art.

To further demonstrate the patentability and allowability of the present claims, Applicant submits herewith a Declaration under 37 CFR 1.132 (and executed toxicology report in Spanish with an English translation) that provides data and evidence establishing that the presently claimed combination of lidocaine, prilocaine and tetracaine provide surprising, unexpected, and/or synergistic results as compared to the single or double anesthetic combinations of anesthetics suggested or taught by the cited state of the art, which the Examiner has cited in prior office actions. Furthermore, the Applicant provide data and evidence demonstrating that the effect is present in all claimed concentration ranges.

In particular, the 132 Declaration (and executed toxicology report in Spanish with an English translation) filed herewith provides direct comparative testing and data establishing that, on comparison of the cited reference compounds with those potentially encompassed by the pending claims in the present application, the one or more unexpected, synergistic, and/or surprising properties (e.g., enhanced anesthetic effect, faster anesthetic effect, decreased adverse effects, increased stability, etc.) of the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, is not taught or suggested to one of ordinary skill in the relevant arts by any one or a properly cited combination of the cited references in the prior Office Actions.

The attached 132 Declaration (and executed toxicology report in Spanish with an English translation) shows that the data in the present specification and 132 Declaration establish that the combination of the three anesthetics (lidocaine, priolocaine, and tetracaine) for a topical anesthetic show surprising, unexpected and/or synergistic properties that cannot be attributable to any additive or separate properties of each or any combination of any two of these anesthetics.

The data in the present specification establish that these surprising, unexpected and/or synergistic properties of the combination of lidocaine, prilocaine and tetracaine, include, inter alia,

(i) surprising, unexpected and/or synergistic <u>enhanced anesthetic effect</u>;

(ii) surprising, unexpected and/or synergistic <u>accelerated anesthetic activity</u>; and/or

(iii) surprising, unexpected and/or synergistic <u>lower adverse effects</u>.

Regarding the surprising, unexpected and/or synergistic (a) enhanced anesthetic effect; (b) surprising, unexpected and/or synergistic accelerated anesthetic activity; and (c) lower adverse effects, paragraphs [0032] – [0037] of the present specification as originally filed summarize a very large clinical study involving 2700 patients ranging in age from 15-65 years of age (see, e.g., [0032]).

Paragraphs [0033] to [0036], and Tables 1, 2 and 3, of the present specification establish that the three anesthetic combination of lidocaine, prilocaine, and tetracaine showed surprising, unexpected and/or synergistic effects as compared to the combination of prilocaine and lidocaine alone.

These surprising, unexpected and/or synergistic effects included (a) enhanced anesthetic effect (as shown, e.g., in Table 1); (b) accelerated anesthetic effect (as shown, e.g., in Table 1); (c) lower adverse effects (as shown, e.g., in Tables 2 and 3).

Thus, the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, shows surprising, unexpected and/or synergistic effects as compared to the cited art, and is therefore not taught or suggested to one of ordinary skill in the relevant arts by any one or a properly cited combination of the cited references in the prior Office Actions.

Additionally, the data as presented in this Declaration (and executed toxicology report in Spanish with an English translation) establish that these surprising, unexpected and/or synergistic properties of the combination of lidocaine, prilocaine and tetracaine, further include, inter alia, surprising, unexpected and/or synergistic greater stability; and/or surprising, unexpected and/or synergistic lower toxicity.

In particular, the attached 132 Declaration (and executed toxicology report in Spanish with an English translation) shows that the surprising, unexpected and/or synergistic greater stability, the following comparative experiments were conducted and analyzed as follows:

> To show that the presently claimed three anesthetic composition provided surprising unexpected and/or synergistic greater stability, the presently claimed three anesthetic topical composition was compared with single and double anesthetic combinations.
>
> In particular, the stability of different combinations of Prilocaine, Lidocaine, and Tetracaine were evaluated by APR laboratory (Applied Pharma Research S.A.)

from March 2008 to March 2009. The following compositions were evaluated, including the use of appropriate standards and controls. The compositions included the following:

1. Batch LCOX/70: TERNARY COMPOSITION LIDOCAINE–PRILOCAINE–TETRACAINE (“LPT”);
2. Batch LCOX/67: TETRACAINE ONLY (“T”);
3. Batch LCOIX/71: BINARY COMPOSITION LIDOCAINE-TETRACAINE (“LT”); and
4. Batch LCOIX/74: BINARY COMPOSITION PRILOCAINE–TETRACAINE (“PT”).

The SCHEDULE OF STABILITY CONTROLS (Time and Temperature), included the following:

	5°C	25°C	30°C	40°C
1 month (T_{1m})		T/LPT		T/LPT
6 month (T_{6m})	T/LPT/ LT/PT	T/LPT/ LT/PT	T/LPT	T/LPT/ LT/PT
12 month (T_{12m})		T/LPT		

The DATA EVALUATED included: (i) Assay and purity of Lidocaine, Prilocaine and Tetracaine; and (ii) known impurities; and unknown impurities.

The analytical methods for assay and purity used for assaying Lidocaine, Prilocaine, Tetracaine, and related impurities at 1 month interval included were the following:

1. M44-07: HPLC Method for Lidocaine, Prilocaine, Tetracaine Assay; and M01-08: HPLC Method for Prilocaine and Lidocaine Purity. With this HPLC method it is possible the identification and the assay of o-toluidine (EP monograph for Prilocaine) and of 2,6–dimethylaniline (EP monograph for Lidocaine). For Prilocaine and Lidocaine were selected the above mentioned impurities because they are the same mentioned in USP 31 NF 26 monography of Lidocaine and Prilocaine cream;
2. M03-08: HPLC Method for Purity of Tetracaine. With this HPLC method it is possible the identification and the assay of 4-butylaminobenzoic acid (US 31 NF 26 monograph for Tetracaine);
3. The above mentioned HPLC methods are supported by “limited Validation” as follows: V01/08: Limited validation for Assay of

Lidocaine, Prilocaine, Tetracaine; V02/08: Limited HPLC Validation for Purity of Tetracaine (4-butylaminobenzoic acid); and V03/08: Limited HPLC Validation Purity of Prilocaine and Lidocaine (o-toluidine, 2,6-dimethylaniline).

Then APR worked to improve analytical methods for assay Lidocaine, Prilocaine, Tetracaine and Tetracaine purity. (Method for Lidocaine and Prilocaine purity was already finalized and so no need to revise). Further investigation on analytical methods for assaying Lidocaine, Prilocaine, Tetracaine and Tetracaine purity and revised methods and validations were then used in order to provide better analytical conditions and to reduce the variability of the assay values obtained, although the variability (CV) of first issue analytical methods (M44-07 and M03-08) was satisfactory.

To find out the better analytical conditions for assaying Lidocaine, Prilocaine, Tetracaine and Tetracaine purity, APR tested different solvent for diluting the analytical sample till find **Acetonitrile** as the best dilution agent. The resulting revisions to these methods include: (a) M44-07 Revision 1: HPLC Method for Lidocaine, Prilocaine Tetracaine Assay; and (b) M03-08 Revision 1: HPLC Method for Purity of Tetracaine. Acetonitrile was discovered to be a better dilution agent than water because it is independent from pH and does not influence the pH of final solution.

The acceptable range of pH for water used as dilution agent in method M44-07, M03-08 was from 5 to 7 in compliance to European Pharmacopoeia; hence the variability in water pH may influence the variability of analytical solution final pH and this gave a high variability (CV) during assay analysis of Lidocaine, Prilocaine and or Tetracaine with M44-07.

Using Acetonitrile as solvent in method for Tetracaine purity may ensure a better and more controlled analysis of 4-Butylaminobenzoic acid formation. Based on these results, APR performed a revision of limited validations for assay and purity methods, including: (i) V01/08 Revision 1: Limited HPLC validation for Assay of Lidocaine, Prilocaine, Tetracaine; and (ii) V02/08 Revision 1: Limited HPLC validation for Purity of Tetracaine (4-butylaminobenzoic acid).

In order to ensure continuity in the analytical results and stability evaluation, stability was tested from the third to the sixth month with both methods; and from the sixth month on, the analysis was performed only with revised method.

PREPARATION AND STABILITY RESULTS OF FINAL FORMULATIONS FOR STABILITY EVALUATIONS

The relative amount of L, P and T is maintained in all the formulations evaluated (the ternary formulation, binary formulations and tetracaine formulation): L 1.5%,

P 1.5% and T 4%. Therefore the effect of an anesthetic on the other ones within a formulation can be compared over all the formulations.

Once the data obtained was revised and studied we could conclude the following:

Stability at 5 ºC:

If we could observe the LPT composition, impurities due to the presence of Lidocaine and Prilocaine are not detected, but impurities from Tetracaine (4-butylaminobenzoic acid) are detected. The impurity from Tetracaine is in the ternary composition in lower values than the values which we can find in the composition with T only.

We could also detect that the values for the unknown impurities are much lower in the ternary composition (LPT) if we compare it with the values detected for the same parameter in the composition with T only.

Finally, in both binary compositions (LT, PT) we cannot find impurities from degradation of Lidocaine and Prilocaine, but we can find impurity from Tetracaine. In this case, the value for 4-butylaminobenzoic acid is bigger than the value found in the Ternary composition and lower than the value detected in the composition of Tetracaine only.

Referring to the unknown impurities we can observe that the values in the binary compositions (PT, LT) are bigger than the ternary composition (LPT) but lower than the composition with Tetracaine only (T).

So, we can conclude that at 5ºC, and in stability terms, the better formulation is the Ternary composition (LPT).

Stability at 25 ºC

We can observe similar results as the ones achieved at 5ºC.

The ternary composition (LPT) presents products from the Tetracaine degradation and unknown impurities at RRt 0.64 and 1.38.

These values are much bigger in the case of the composition with Tetracaine only during the time of the research at these temperature conditions.

For binary compositions (PT, LT) the values of the known and unknown impurities are similar. These values are bigger than the ternary composition and lower than the composition with T only.

Then, at these temperature conditions, we can conclude that the ternary composition is the better from an stability point of view.

Stability at 30 ºC

The results in the ternary composition continue in the same line of the others temperature conditions.

The results are much bigger in the composition with T only.

We have no data for the binary compositions (LT, PT).

Stability at 40 ºC: At this temperature, we control accelerated stability, so it is normal that at this conditions the product becomes unstable.

Evaluating the results obtained in the binary compositions or in the product with Tetracaine only, it can be assumed that the instability at 40 ºC is strictly due to Tetracaine.
The gel with Tetracaine only is less stable than the binary composition with Tetracaine and than the ternary blend, being the last one the best one in stability terms.

From a stability point of view and after analyzing the whole data obtained during this year we can conclude that Prilocaine and Lidocaine stabilize Tetracaine when they are in the same formulation.

The above results clearly demonstrate that the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, shows surprising, unexpected and/or synergistic increased stability as compared to single or double anesthetic compositions, such as those suggested or taught by the cited state of the art. This is clearly shown by the surprising, unexpected and/or synergistic decreased presence of known and unknown impurities with the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, as compared to single or double anesthetic compositions.

Thus, the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, shows surprising, unexpected and/or synergistic effects as compared to the cited art, and is not taught or suggested to one of ordinary skill in the relevant arts by any one or a properly cited combination of the cited references in the prior Office Actions.

Additionally, the data as presented in the 132 Declaration (and executed toxicology report in Spanish with an English translation) "establish that these surprising, unexpected and/or synergistic properties of the combination of lidocaine, prilocaine and tetracaine, further include, inter alia, surprising, unexpected and/or synergistic lower toxicity.":

Regarding the surprising, unexpected and/or synergistic lower toxicity, the following comparative experiments were conducted and analyzed as follows.

To show that the presently claimed three anesthetic composition provided surprising unexpected and/or synergistic lower toxicity, the presently claimed three anesthetic topical composition was compared with single and double anesthetic combinations.

In particular, the toxicity of different combinations of Prilocaine, Lidocaine, and Tetracaine were evaluated, including the use of appropriate standards and controls.

The objective of this research is to demonstrate the synergistic effect in the decreasing of the adverse effects when we use a combined anesthetic with Lidocaine (L), Prilocaine (P) and Tetracaine (T), compared with each ingredient alone and in the same total concentration.

The following design parameters are taken into account: in order to have a valid comparison, the compositions have to maintain the same total amount of anesthetic in each composition which is going to be compared; and
Testing different ranges of concentration according to claims of the patent application.

The 24 anesthetic compositions to be tested are the following:

1) The lower concentration range which is claimed: 0.5L + 0.5P + 0.5T (1.1), compared with: 1.2) 1.5L; 1.3) 1.5P; and 1.4) 1.5T;

2) The higher concentration range which is claimed: 5L + 5P + 8T (2.1), compared with: 2.2) 18L; 2.3) 18P; and 2.4) 18T;

3) Composition 1.5L + 1.5P + 4T (3.1), compared with: 3.2) 7L; 3.3) 7P; and 3.4) 7T

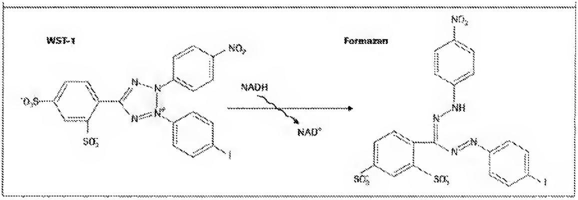
4) The presently claimed Ternary composition which keeps the same proportion of each agent as the above mentioned point (1.5L + 1.5P + 4T), but with a total sum of the anesthetic similar to EMLA and AMLI (5 parts of total anesthetic). In the same way two other ternary combinations will be tested which keep the total sum of anesthetic equal to EMLA and AMLI (5 parts): 4.1) 1.07L + 1.07P + 2.86T; 4.2) 1.5L + 1.5P + 2T; and 4.3) 1.5L + 2P + 1.5T,
compared with: 4.4) 5L 4.5) 5P; 4.6) 5T; 4.7) 2.5L + 2.5P (EMLA); and 4.8) 2.5L + 2.5T (AMLI).

5) Composition 1.5L + 1.5P + 8T (5.1) compared with: 5.1) 11L; 5.2) 11P; and 5.3) 11T.
(Concentrations of each anesthetic are in % w/w.)

MATERIALS AND METHODS: In order to compare the abovementioned we study the cytotoxicity of these 24 anesthetic compositions on CaCO-2 cells (human epithelial cells) by determining cell viability through WST-1. The study was carried out 24 hours after the treatment with the different anesthetic compositions, and four independent tests were done in triplicate.

The cytotoxic effect of a compound is determined by evaluating the percentage of cell death which the compound produces in comparison with a group of control

cells which have not been treated. In order to do this, cell viability is measured by determining metabolic activity through a WST-1 (Roche) test. This method is based on the capacity of cells to obtain the energy necessary in order to continue their functions and to produce cell growth. For this reason, cells which are metabolically active (alive) reduce tetrazolium salts to formazan by means of the enzyme succinate-tetrazolium reductase (of the mitochondrial respiratory chain). The resulting formazan can be detected colourimetrically (see Figure 1). In contrast, this reaction does not occur with damaged or dead cells.



Chemical reaction produced by the enzyme succinate-dehydrogenase of the mitochondrial cell chain. Formation of formazan from WST-1.

In the first instance, a preliminary test was carried out in order to determine the optimum working concentration which would allow differences to occur in the cytotoxicity of the different anesthetic compositions, as well to verify that the excipient used would not, itself, produce toxicity. A first test was carried out in which the anesthetic compositions were diluted 1:10 in the growth medium. This caused the death of all the cells within a few hours after treatment. A second test was then carried out in which the anesthetic compositions were diluted 1:1000 in the growth medium. This provided appropriate results in order to be able to carry out a comparison between the anesthetic compositions.

Due to the viscosity of the anesthetic compositions, various tests were done in order to determine the procedure which would make reproducing the results the easiest. In the end, a dilution of 1:10 in cell growth medium was chosen. This was done 24 hours before the experiments were carried out in order to homogenize the dilution. At the time of the test, and after tempering the preparation, a second dilution of 1:100 in complete growth medium was carried out.

RESULTS: 24 anesthetic compositions were tested on CaCO-2 cells in a final optimum dilution of 1:1000 of the cell medium. Toxicity was analyzed by

measuring metabolic cell activity in (untreated) control cells and cells treated with the anesthetic compositions.

The table above shows the average percentage of toxicity caused by the anesthetic compositions on the CaCO-2 cells after 24 hours of treatment, compared to the (untreated) control cells. The averages given here are the averages of four independent tests carried out in triplicate. The standard deviation (SD) is given as well as the standard error of the mean (SEM). The p-value of the Student t-test is also given for each group of samples compared with the reference (REF) in each case. Differences are significant for p<0.05 (5.0E-02).

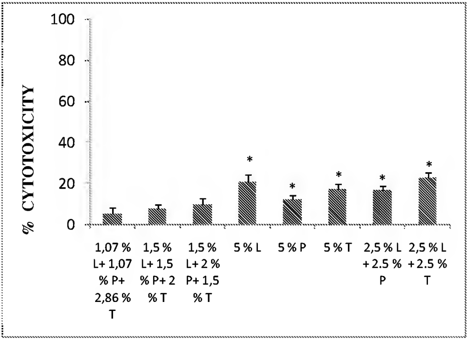
Composition	Samples		Medias	SD	SEM
EXCIPIENT		6	9	3	
0,5% L+0,5% P+0,5% T	1.1	2	8	2	REF.
1,5 % L	1.2	3	5	2	4,4E-01
1,5 % P	1.3	5	7	2	1,9E-01
1,5 % T	1.4	6	10	3	1,7E-01
5% L+ 5% P+ 8% T	2.1	23	16	5	REF.
18 % L	2.2	25	16	5	3,8E-01
18 % P	2.3	20	20	6	3,7E-01
18 % T	2.4	64	16	5	1,0E-06
1,5% L+1,5% P+4% T	3.1	42	17	5	REF.
7 % L	3.2	44	15	4	5,0E-01
7 % P	3.3	44	20	6	4,7E-01
7 % T	3.4	56	18	5	5,1E-02
1,07 % L+ 1,07 % P+ 2,86 % T	4.1	5	10	3	REF.
1,5 % L+ 1,5 % P+ 2 % T	4.2	8	8	2	2,5E-01
1,5 % L+ 2 % P+ 1,5 % T	4.3	10	11	3	1,6E-01
5 % L	4.4	21	11	3	8,7E-04
5 % P	4.5	12	7	2	3,3E-02
5 % T	4.6	17	9	3	3,5E-03
2,5 % L + 2.5 % P	4.7	17	7	2	2,6E-03
2,5 % L + 2.5 % T	4.8	23	7	2	4,6E-05
1,5% L + 1,5% P + 8% T	5.1	22	13	4	REF.
11 % L	5.2	22	10	3	4,5E-01
11 % P	5.3	16	12	3	1,2E-01
11 % T	5.4	50	17	5	2,5E-04

CONCLUSIONS: A cytotoxicity study was carried out on 24 anesthetic compositions in a cell culture: CaCO-2. The results indicate, in the first instance, that the excipient (in the dilution used) displays no toxicity in the cell cultures.

The results obtained, therefore, are due entirely to the effects of the different anesthetics. The result which stands out the most in the test carried out is the higher toxicity of the T anesthetic composition, while the L and P anesthetics presented lower toxicity, their results being quite similar.

In all cases the ternary combination of anesthetics (L,P,T) presents a lower toxic level than any of them separate. It is especially notable when we compare the ternary combination with T alone.

Below we can see the graphic representation of these results:



As we can see in the figure above, in all studied cases, the ternary anesthetic combination presents a lower toxicity level compared with the rest of the samples.

From this information one of ordinary skill in the art would conclude that a three anesthetic combination (L, P, T) presents a surprising, unexpected, and/or synergistic lower toxicity in human epithelial cells than the anesthetic EMLA and AMLI in the same total sum of anesthetic (5 parts).

Applicant also points out that the assay and comparative testing data and results (in both the attached 132 Declaration and in the specification as filed) establish both unexpectedly lower toxicity and lower adverse effects than the use of single or double anesthetic combinations compared to the claimed triple anesthetic compounds. Thus,

the assay data can be considered as further support for unexpected results shown in both the specification and 132 Decalration. Applicant also points out that the comparative data and evidence were present in all of the claimed concentration ranges.

Thus, the claimed triple anesthetic composition comprising lidocaine, prilocaine and tetracaine, shows surprising, unexpected and/or synergistic effects as compared to the cited art, and is not taught or suggested to one of ordinary skill in the relevant arts by any one or a properly cited combination of the cited references in the prior Office Actions.

CONCLUSION

The Notice of Allowance of August 16, 2010, is obviated; however, upon consideration of the attached IDS and amendments, Applicant respectfully requests that a timely Notice of Allowance be issued in this case. Applicant believes no fees or petitions are due with this filing, apart from the fees for the filing of a Request for Continued Examination. However, should any such fees or petitions be required, please consider this a request therefore and authorization to charge Deposit Account No. 02-2093 as necessary. The Examiner is invited to contact the undersigned should the Examiner believe it would expedite prosecution.

Dated: December 03, 2010

Respectfully submitted,

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